

ETHICAL CONSIDERATIONS OF THE USE OF INVESTIGATIONAL NEW  
DRUGS DURING THE GULF WAR

BY

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## ABSTRACT

At the onset of the Gulf War in 1992, the threat of chemical and biological weapons prompted the Department of Defense to seek a waiver from the Food and Drug Administration to use the investigational new drugs pyridostigmine bromide and botulism vaccine without first obtaining consent from those servicemen and women who would receive the drugs. The waiver was granted and came in the form of the Interim Rule, which permitted the use of investigational new drugs when consent could not be obtained because of “non-feasibility” and the nature of the military mission. The Interim Rule restricted the soldiers’ rights to informed consent, but was it justified?

In this thesis, I examine the reasoning behind the use of investigational new drugs and conclude that the Department of Defense had no choice other than to give the soldiers the investigational new drugs without their consent. I first establish that the use of the investigational new drugs constituted therapy rather than research due to the drugs’ established safety record and intent of the Department of Defense in administering the drugs. Secondly, through a critique of the ethical reasoning behind the use of investigational new drugs, I contend that the bioethical principles of beneficence and non-maleficence compelled the Department of Defense to administer the drugs without consent. In so doing I provide an ethical defense of the Interim Rule. Finally, I offer alternatives to the Interim Rule including revocation and anticipatory consent. I conclude by providing information on the current status of the Interim Rule and by discussing its shortcomings.

## INTRODUCTION

While commanding his forces in February of 1777, General George Washington faced smallpox crises that destroyed his army at Valley Forge (1). Faced with the decimation of his troops and inevitable defeat, Washington ordered mandatory smallpox vaccination of those soldiers who had not had been infected before (1). The process of inoculation was quite new in America and carried the risk of death and disease (2, 1). Among those inoculated, about two percent of soldiers died from exposure to the smallpox virus after inoculation, while others became seriously ill (1). When considering these factors, Washington decided it was necessary to vaccinate his army (2). The vaccination was required in the interest of national security—either inoculate or lose the war. Therefore, the soldiers were not asked to consent to the inoculation and forcibly given the vaccine (2). The forcible vaccination helped combat the intentional spreading of smallpox by the British Army and allowed the United States Army to win the Revolutionary War (3, 2).

Soldiers sacrifice many of their freedoms upon enlisting in the military. As evidenced above, the military has a history of exploiting this relationship in order to achieve its objectives and goals. More recently, in 1958, Master Sergeant James Stanley voluntarily participated in a program to test the effectiveness of protective clothing against chemical weapons (4). Without his consent or knowledge, Stanley was secretly given doses of lysergic acid diethylamide (LSD) by the Department of Defense (DoD) and the Central Intelligence Agency (5, 4). Stanley was given these doses to study the effects of LSD on humans, as it was believed at the time that the Soviet Union was

looking to explore its uses as a chemical weapon (4). The ingestion of LSD prompted Stanley to suffer hallucinations, incoherence and memory loss for prolonged periods of time (4). Furthermore, “without reason, [Stanley] violently beat his wife and children, later being unable to recall the entire incident” (5). Stanley was soon discharged from the military in 1969 after his performance greatly suffered (4). Stanley was not aware that he had been given LSD until 1978, when he received a letter from the Army requesting his participation in a follow-up study (4, 5). The LSD studies illustrate how those serving in the military are a vulnerable population that can be taken advantage of under the guise of national security and the needs of the military. The possibility of exploitation, however, became even more prevalent when soldiers received investigational new drugs (INDs) from the Food and Drug Administration (FDA) without their consent during the Gulf War.

In the 1990’s, when it was apparent that the crisis in the Gulf was going to lead to war with Iraq, military planners looked at the very real possibility of Iraq’s ability to use chemical and biological weapons in warfare (1). Iraq’s president, Saddam Hussein, had used chemical and biological weapons in the past against Iran in the Iran-Iraq War and American planners believed that he had the capability of using them against U.S. forces (1). This threat prompted the DoD to seek a waiver of consent from the FDA in order to allow the use of the INDs, pyridostigmine bromide (PB) and botulism vaccine on troops without their informed consent, as obtaining informed consent was seen as “not-feasible” (6, 1).

Before deploying troops for combat, the FDA granted the DoD’s waiver request and passed an Interim Rule amending the prior regulations (4). The Interim Rule allowed

for the waiving of individual consent from military soldiers for a “specific military operation involving combat or the immediate threat of combat” (7). Soon after the amendment and waiver, the drugs were distributed to hundreds and thousands of soldiers who engaged in battle in the Middle East (8). However, INDs, as their name suggests, have not been proven to be effective and the forced administration of these drugs raises ethical questions regarding the obligation to obtain informed consent in the military.

In this thesis, I will consider the ethical implications of the forced use of INDs in the Gulf War, which was made possible by the Interim Rule. More specifically, I will determine whether the use of INDs created an informed consent obligation that the DoD overlooked. In order to determine whether the DoD was within its bounds to administer the INDs without consent, I will first look at the Gulf War scenario and the need for INDs. Second, I will examine the history and significance of informed consent and the history of the use of INDs as therapies. Third, the ethics of waiving consent for unproven therapies and the DoD’s obligation to its troops will be discussed. In conclusion, I will discuss alternatives to the Interim Rule that may balance the rights of soldiers with the objectives of the military.

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## CHAPTER ONE

### THE GULF WAR AND THE INTERIM RULE

In this chapter, I will first examine the start of the Gulf War and the need for pre-exposure therapies. I will then discuss the need for and passing of the Interim Rule. The case of *Doe v. Sullivan*, which quickly challenged the Interim Rule, will then be examined. Finally, I will conclude the chapter with a brief literature review on the Interim Rule. This chapter will demonstrate the need for the Interim Rule and why the DoD had to administer the INDs without obtaining informed consent.

#### ***Gulf War***

Iraqi forces led by Saddam Hussein on invaded and easily occupied the oil-rich gulf state of Kuwait August 2, 1990 (1). The Iraqi leader always believed that Kuwait was part of Iraq and he was trying to reclaim what he thought was his rightful territory (2). As soon as news spread around the world of Hussein's offensive, the United Nations Security Council (UNSC) quickly and unanimously adopted Resolution 660, which "1. Condemn[ed] the Iraqi invasion of Kuwait; 2. Demand[ed] that Iraq withdraw immediately and unconditionally all of its forces to the position in which they were located on 1 August 1990" (3, 1). After Hussein refused to withdraw his troops, the UNSC adopted Resolution 661, reaffirming Iraq's transgressions in the hopes of avoiding military confrontation (4, 1). This was quickly followed by Resolution 665 which authorized a naval blockade to enforce the economic sanctions against Iraq (1). However, with Iraqi troops still occupying the sovereign state of Kuwait, the UNSC

issued Resolution 678 in late November 1990, which established a deadline of January 15, 1991 for Iraq to withdraw (5, 1). The failure to withdraw would result in the use of “all necessary means to uphold and implement” the withdrawal of Iraqi forces—thus providing legal authorization for war (5, 1). As Iraqi forces continued to defy the Security Council’s requests to leave Kuwait and a further invasion of Saudi Arabia loomed, the prospect of war became imminent (1, 2).

In order to prevent Saddam Hussein from invading Saudi Arabia and taking over the majority of the world’s oil reserves, President George H. Bush authorized a deployment of soldiers in a “wholly defensive” operation called Desert Storm (2, 1). In this operation, more than half a million U.S. military personnel were deployed to Saudi Arabia, and a broad coalition of forces was assembled for anticipated military action to force the withdrawal of Iraqi troops from Kuwait (1, 2).

American military planners who headed the coalition faced the task of confronting Saddam Hussein’s army, one of the largest of the world at the time (6, 2). The military planners were particularly concerned with the vast array of chemical and biological weapons believed to be in possession by the Iraqis (8, 1). It was widely speculated that Iraq had possessed biological and chemical weapons in the past as Hussein had used them against Iranian troops during the Iran-Iraq War (6). According to one estimate, Iraq was capable of producing up to 2,000 tons of nerve gas and 3,500 tons of mustard gas that could affect soldiers through inhalation (8, 1). The agents identified by the military planners included tabun, sarin, and soman (1). These inhalation agents were thought to pose the biggest threat to the soldiers (6, 1). The agents acted by “irreversibly bind[ing]” and inactivating the enzyme acetylcholinesterase (AChE) (1).

This enzyme is vital to bodily functions, as it allows the body's muscles to communicate with the nerves (6). When the enzyme is inhibited, a variety of symptoms occur that include incapacitated muscle movement which eventually leads to respiratory arrest (and death, if not treated) because of muscle failure (6, 1). A lethal dose of the agent can be "as small as 1 mg" and "even the best trained soldiers" cannot avoid inhaling up to five times that amount in the event of an attack (1).

The U.S. military prepared for biological and chemical attacks by adopting several defensive measures including, but not limited to:

- 1) Individual and collective protective equipment....such as chemical/biological mask[s] protective equipment such as chemical and biological masks,
- 2) Equipment for detecting chemical agents in the environment
- 3) Specific countermeasures to be used before or after an attack, such as the Mark 1 Nerve Agent Antidote Kit

(1)

Even with all these defensive measures and protections, the DoD did not have any preventative pre-exposure therapies to help decrease the lethality of these agents (1).

The need for pre-exposure preventative measures is evident upon examining the situations in which the soldiers would have encountered the chemical and biological weapons. For example, in order to first prepare for the possibility of the use of chemical weapons, the military first needed to detect the presence of the chemical and biological agents (1). In order to detect these agents, the military had to set up the detection equipment upwind and ahead of the unit, which made it highly unsuitable for mobile offensive operations (1). In fact, the equipment was not even capable of quickly detecting and identifying the chemical agents, but instead samples needed to be sent to remote field laboratory in order to be tested (1). This delay in identifying agents could severely

increase the number of fatalities and injuries from chemical and biological weapons (6, 1).

Furthermore, even if nerve agents were detected early enough, soldiers were still at serious risk of disability and death because of their inability to implement proper countermeasures (1). The first couple of minutes after exposure are the most vital in providing an antidote when one has been exposed to a chemical weapon because the short half-lives of the chemicals enable them to break down in the body quickly (8). After the first couple of minutes, the antidotes may become ineffective in preventing further injury (9). For this reason, exposed soldiers had to be administered a post-exposure therapy of repeated injections of the antidotes atropine and 2-PAM (7, 1). The units at the front lines, who were engaged in battle, would have found it very difficult to administer such constant aid (1). This would have been especially difficult since these units have very little, if any, medical assistance (1). More so, if ventilators were required for exposed units, this entailed immediate evacuation and mass transport of units to field hospital which is a logistical nightmare in times of war (1). For these reasons, identifying pre-exposure drugs that would help delay and counteract the effects of nerve and biological agents was ideal in helping the military carry out their missions against Iraq.

### ***Pre-exposure Therapies Identified***

In order to help protect soldiers from the effects of chemical and biological weapons, the DoD selected two drugs that could be given to soldiers as pre-treatments: the first, pyridostigmine bromide (PB) and second, a botulism vaccine (8). PB is an acetylcholinesterase (AChE) inhibitor that was believed to be effective in treating soman,

one of the four deadly nerve agents identified by military planners (8). PB acts by inhibiting AChE, thereby preventing the soman from binding to and harming the enzyme (8). At the dosage prescribed by the DoD, one 30 mg tablet every eight hours, it is estimated that about 20-40% of AChE's are inhibited (1, 8). Even with the prescription of PB the immediate administration of atropine antidotes is required to help counter any remaining nerve agents post-exposure and reduce the harm incurred from soman (1, 8). The recommendation for the use of the PB was based on animal testing that provided evidence that PB, when used in conjunction with post-exposure antidotes, helps provide a significantly higher level of protection than just the post-exposure antidote by itself (1, 8).

The efficacy of PB was measured using protection ratios (PR) (8). The PR reflects the ability of the drug to provide protection against a median lethal dose of the control group (1, 8). For example, a PR of 5.0 means that the protection against nerve agents is five times higher than having no intervention and is considered a "reasonable level of effectiveness" (10). Likewise, a PR of 1.0 indicates that the compound is ineffective in protecting the group, since the dose of the control group is still lethal (10). A study among rhesus monkeys exposed to soman with a pretreatment of PB and a post-exposure antidote showed a PR of more than 40.0 when compared to just a post-exposure antidote which had a PR of 1.4 (11, 1). This study helps illustrate the low effectiveness of post-exposure antidotes by themselves and the need for an effective pretreatment. However, the effects of a pretreatment on humans and other species are not necessarily the same as those on rhesus monkeys because of the variability in different species (1). In testing the effectiveness of PB in rabbits and mice, the increase in PR was minimal and even

statistically insignificant when compared to the effectiveness of post-exposure antidote alone (10, 1). Even so, the DoD still went ahead in recommending the drug for use by soldiers because the use of PB may still lessen the harm from chemical agents.

However, the DoD was not able to prescribe PB and botulism vaccine to soldiers as pre-exposure treatments since they were classified as INDs. Section 505 of the Food and Drug Cosmetic Act prohibits the introduction of a new drug until it has been shown to be both “safe in use” and “effective in use” (12). INDs are licensed only for specific uses and only with the consent of the recipient; thus, the DoD was prohibited from using PB and botulism vaccine without obtaining the consent of the soldiers that would receive it. This is why the DoD sought out the Interim Rule.

### ***The Interim Rule***

The Interim Rule was born out of necessity. Since the DoD could not give INDs to the soldiers without their informed consent, the Interim Rule was created to enable the DoD (through the FDA) to use unapproved drugs for specific combat purposes. This section will examine the history of the Interim Rule and the rationale for passing it.

The Food Drug and Cosmetic Act (FDCA), originally enacted in 1938, authorized the Secretary of Health and Human services to regulate all processes of drug approval in the United States (12, 13). The Secretary then delegated this power to the Commissioner of Food and Drugs and the Food and Drug Administration (FDA). Thus, the FDA became responsible for oversight of the development, testing, and evaluating of all drugs, vaccines and medical equipment used in interstate commerce (13). The Food and Drug Cosmetic Act prohibits the introduction of any drug (regardless of status) into interstate

commerce until it has been approved by the FDA as “safe for use” and “effective for use” (12). The criteria for determining drug safety are based on conducting “adequate tests by all methods reasonably applicable” (12). Effectiveness of a drug is based on "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the purposed labeling thereof” (12). Therefore, drugs are considered effective if they do what they are purported to do when used as recommended.

The current FDCA dictates that the Secretary of Health and Human Services is required to issue regulations exempting those drugs “intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs” (12). These regulations require that “before any clinical testing of a new drug is undertaken,” sponsors of the study must file with the FDA an IND application, in which the sponsors agree on supervising the investigators, keeping adequate records and reports, and obtaining written informed consent from each participant of the trial (15, 16). These IND regulations cover the first three phases of clinical drug trials (including those of safety and then effectiveness). After the sponsor of the drug research has found adequate evidence of safety and efficacy, a New Drug Application (NDA) is submitted to the FDA (13). If the FDA approves the drug, it may be used only for the specific use or indications that it was approved for. If the drug has not yet been approved for a specific purpose, it cannot be used in clinical trials without proper informed consent (13).

The drugs in question, PB and the botulism vaccine, were classified by the FDA as INDs, and were licensed only for specific uses. PB was licensed for only two civilian

uses (8). The FDA first approved it in 1955 as a treatment for myasthenia gravis, a debilitating neuromuscular disease (8). At the time, the average daily dose prescribed for the treatment of myasthenia gravis was as much as six times greater than the dose the DoD sought to administer to soldiers (8). The FDA later approved the use of PB for treatment in reversing some of the side effects of anesthesia, such as reversing neuromuscular blockers (8).

In 1990, when the DoD sought to use PB, it had never been approved as a pretreatment against nerve agents, although it had been investigated for this use since 1984 when the US Army filed an IND application with the FDA (13). The safety of PB was established by the military through over 25 studies in humans and animals, some lasting as long as 34 weeks (1, 8). The claims of efficacy, however, were based solely on animal studies (8).

The botulism vaccine was also labeled as investigational during the time of the Gulf War. The botulism vaccine was considered safe since persons at risk of contracting botulism (such as farmers) had been routinely using the vaccine since the 1980's (13). However, since the threat of botulism is minor and not likely to increase, there are no commercial sponsors for the vaccine and it remains unlicensed as an IND (13). Though the vaccine had been used before for purposes of immunization, the FDA had not approved the botulism vaccine as a pre-treatment in case of a biological attack. Since there was no way to avoid the FDA regulations, the DoD had to consider other means of obtaining consent or waivers so the INDs could be given to soldiers (13).

The DoD had to work with the FDA to find a solution, and the two branches of government have a history of working together well (13). A Memorandum of

Understanding (MOU) has existed between the DoD and the FDA since 1987 and pertains to the "investigational use of drugs, antibiotics, biologics, and medical devices" (15). This MOU asserts that any clinical testing of investigational drugs sponsored by the DoD, or with the help of the DoD, will follow FDA regulations governing "the investigational use of new drugs and medical devices in human beings" and furthermore that the testing will fully adhere to FDA's Investigational Review Board (IRB) and informed consent regulations (15, 16).

The FDA requirements include adhering to the "Common Rule" (45 C.F.R. 46) when conducting research. The Common Rule applies to all federal agencies that sponsor research and requires Institutional Review Boards (IRBs) to review and approve all research protocols that involve human subjects. The IRB has to evaluate each protocol to ensure the following: 1) risks to subjects are minimized; 2) risks to subjects are reasonable in relation to anticipated benefits; and 3) informed consent will be sought from each subject in accordance with the general requirements for informed consent (16). The MOU ensured that the DoD and its IRBs would follow the same protocols as other federal agencies when conducting research (13).

As Iraq invaded Kuwait, military planners immediately concluded that there was a need to use INDs without obtaining informed consent (13, 1). The DoD examined solutions and concluded that the requirements of informed consent "in armed conflict and in circumstances of potential armed conflict for deployed and deployable units . . . could not be met" and that it had to obtain waivers in order to use the INDs (17). However, in order to use INDs with waivers of consent, the DoD had to address two issues regarding them: first, whether or not the use of INDs without consent violated Title 10 U.S.C. §

980, and second, whether or not the FDA could create an amendment that informed consent is “not feasible” in certain military situations and waivers could be granted (18, 13).

Title 10 U.S.C. § 980 was added to a DoD appropriations bill in 1972 and stated that appropriated funds cannot be used “for research involving a human being as an experimental subject unless the informed consent of the subject has been obtained in advance or, in cases of research intended to benefit the subject, the informed consent of the subject or a legal representative” is obtained in advance (18). The DoD addressed this problem in a memo by stating that the INDs that were to be used in this situation were not “remarkably novel nor experimental in a scientific or medical sense” (19). The DoD further argued that some of the INDs had been subjected to “extensive research” (over 25 years in the case of PB) and should not be considered research (19, 13). Furthermore, the memo stated, “it is clear that the proposed uses are not in any usual sense of the word for ‘research’ purposes, but rather to assure the best possible preventative and therapeutic treatment possible for all contingencies presented” (19).

The DoD stated its position (in regard to the use of INDs not being considered research) by saying that the drugs had “progressed through the FDA's IND process sufficiently to establish a high level of confidence on part of the DoD medical community” (19). Moreover, there was a DoD directive in 1983 on the “Protection of Human Subjects in DoD Research,” which stated that research is “a systematic investigation... designed to develop or contribute to generalizable knowledge” (20). This directive authorized the military departments to determine which “unique military requirements dictate the use of drugs or devices not officially approved by the FDA”

(20). Regardless of whether the INDs were considered research or therapy, the DoD still needed to obtain informed consent in order to administer them since the FDA regulations allowed their use only for approved uses. The DoD turned to the FDA in hopes of getting an amendment approved that would allow for the waiver of consent.

The FDA agreed that a new rule should be written to help determine that informed consent was “not feasible” in certain military situations since it could be used in the future on a case-by-case basis (13). With the creation of a new rule, the FDA would be able to look at proposed DoD applications for waivers that explained why unapproved drugs could be used and why consent was not feasible. This would allow the FDA to subsequently grant the waiver for a limited amount of time as necessary for military needs.

On October 30, 1990, the Assistant Secretary of Defense for Health Affairs, Dr. Enrique Mendez, sent a letter to the FDA that sought to obtain a waiver from the FDA on grounds that there was no other suitable treatment and it was “not feasible” to obtain informed consent (21, 1). The Assistant Secretary for Health Affairs at the Department of Defense wrote to the Department of Health and Human Services that:

FDA assistance is also need on the issue of informed consent. Under the Federal Food, Drug and Cosmetic Act, the general rule is that, regardless of the character of the medical evidence, any use of an IND, whether primarily for investigational purposes or primarily for treatment purposes, must be preceded by obtaining informed consent from the patient. The statute authorizes exceptions, however, when the medical professional administering the product deem it not feasible to obtain informed consent.

(21)

The same letter submitted on October 30, 1990 argued that obtaining informed consent was not a feasible option due to the nature of the military:

In all peacetime applications, we believe strongly in informed consent and its ethical foundations. In peacetime applications, we readily agree to tell military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that refusal to participate will involve no penalty. But military combat is different. If a soldier's life will be endangered by nerve gas, for example, it is not acceptable from a military standpoint to defer to whatever might be the soldier's preference concerning a preventive or therapeutic treatment that may save his life, avoid endangerment of the other personnel in his unit and accomplish the combat mission. Based on unalterable requirements of the military field commander it is not an option to excuse a non-consenting soldier from the military mission, nor would it be defensible militarily—or ethically—to send the soldier unprotected into danger.

(21)

In the letter, the DoD stated that allowing soldiers to refuse the drugs (PB and botulism vaccine) would increase the threat of battlefield casualties due to lack of protection. The refusal of some soldiers to consent would pose a greater burden upon those that did have the pre-treatment agent since those who did not have a pre-treatment agent such as PB would be at greater risk of death and disease. Mendoza went on to state that there were a number of Supreme Court cases that had established “that special military exigencies sometimes must supersede normal rights and procedures that apply in the civilian community” (21, 13). Therefore, the obtaining of informed consent was “not feasible” since a soldier who refused the INDs (PB and botulism vaccine) would threaten the objectives of the military and endanger the lives of his fellow soldiers.

Soon after the petition, the FDA approved the DoD's request on December 21, 1990, and amended 21 C.F.R. 50.23. This amendment became known as the “Interim Rule” (22). The Interim Rule determined that if informed consent was not feasible, it was not a necessary prerequisite to treating soldiers with investigational drugs during a “specific military operation involving combat or the immediate threat of combat” (22). This authority to grant the waiver for the use of INDs rested on the FDA commissioner who could waive this requirement “when withholding treatment would be contrary to the

best interests of military personnel and there is no available satisfactory alternative therapy” (23).

On December 28, 1990, the FDA Commissioner, David Kessler, received the official requests from Dr. Mendez to determine “that obtaining informed consent is not feasible because of military combat exigencies” (21). This request was forwarded to the FDA’s Informed Consent Waiver Group (ICWRG) which, after reviewing the requests for waivers, recommended approvals of the drugs PB and botulism on January 8, 1991 (24, 13). However, the group warned, “efficacy data are based wholly on studies in animals” and therefore could not be fully trusted (27, 13). The FDA Commissioner at the time agreed with the recommendations, and under his authority signed the waivers of informed consent for the use of botulism vaccine to be used to immunize against the threat of botulism and for PB to be used as a pretreatment for chemical weapons (13). Both of the drugs were limited to a 12-month period (13). After these waivers were approved, PB was distributed to nearly 700,000 soldiers (25). The majority of the soldiers who took PB were told that they had no choice in the matter. In contrast, the botulism vaccine, according to the DoD, was optional and offered on a voluntary basis (25). It is estimated that 8,000 people received the botulism vaccine (25). However, once again, about 80% of those who received the vaccine were told that they were given no choice in the matter (25). The Interim rule was not without controversy. The forced administration of INDs drew immediate protests from some soldiers. One such soldier was John Doe (anonymous) who took the DoD to court.

***Doe v. Sullivan***

Immediately following the issuance of the Interim Rule and the waivers of consent, a lawsuit was filed in the United States District Court for the District of Columbia on January 31, 1991. The lawsuit sought to prohibit the DoD “from using unapproved drugs on troops taking part in Operation Desert Storm without first obtaining informed consent from the individual military personnel” (26). The plaintiff, John Doe, was a serviceman stationed in Saudi Arabia during the Gulf War who brought a lawsuit against Louis Sullivan, the Secretary of Health and Human Services and Richard Cheney, Secretary of Defense. The lawsuit alleged that: 1) the Interim Rule (FDA Rule 23 (d)) was outside the authority of the FDA under section 505(i) of the FDCA regarding feasibility of consent; 2) the DoD’s use of investigation drugs without obtaining informed consent violated the Defense Department Authorization Act (10 U.S.C. § 980); and 3) the Government’s use of drugs on a person who did not consent was a violation of the person’s Fifth Amendment right to Due Process (27, 16).

The first accusation arose out of the FDA’s scope of judging the feasibility of consent (27). The FDA is in charge of enforcing the FDCA, which provides guidelines for the approval of drugs. The FDCA forbids the introduction of new, unapproved drugs into interstate commerce unless those drugs are “intended solely for investigational use” and can be used in serious or life-threatening conditions for treatment purposes (12). The FDCA further mandates, that informed consent be obtained for the use of investigational drugs unless the consent is deemed “not feasible” (12).

Consent is generally defined as not feasible when (all conditions must be met):

- 1) the human subject is confronted by a life-threatening situation;

- 2) informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject;
- 3) time is not sufficient to obtain consent from the subject's legal representative;
- 4) there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject

(12).

These definitions of feasibility, however, are pertinent to the condition of the individual and not the surrounding circumstances (27). The Interim Rule expanded the definitions of feasibility to include situations where there is actual or a threat of military combat rather than situations where consent is not feasible. Therefore, in his first accusation Doe alleged that the FDA was out of its scope in defining and expanding the definition of the “non-feasibility” of consent (26).

In his second allegation, Doe claimed that the Defense Authorization Act prohibited the use of DoD funding for research on human subjects without prior informed consent. While the FDCA contained exceptions, the DoD did not have any exceptions for the conducting of research without the subject's consent (27). Therefore, Doe alleged that research was being carried out with the use of INDs and the DoD should obtain consent in advance.

Finally, Doe's last allegation stated that the use of INDs without informed consent violated Doe's right to due process. In examining this charge, the court had to determine whether the constitutional rights of the plaintiffs were violated by not obtaining consent (27). If the violation is tied to state interests then courts will examine whether the law “significantly interferes with the exercise of a fundamental right . . . [and] cannot be upheld unless it is supported by sufficiently important state interests” (27).

After filing the lawsuit challenging the Interim Rule, the United States District Court for the District of Columbia dismissed all three charges (13). In his ruling, Judge Harris ruled in favor of the defendant by first holding that the plaintiff's case was not likely to hold up in court because the use of unapproved drugs was a "military decision" and that a long line of cases supported the defendants' claim that the courts should not interfere with the relationship between the military and its personnel (29, 16). He further stated that the "complex, subtle and professional decisions as to . . . training, equipping and control of the military force are essentially professional military judgments, subject always to civilian control of the Legislative and Executive Branches." Judicial interference "in this type of strategic decision," Judge Harris stated, would be ill-suited (26, 27).

On the first issue of whether or not the Interim Rule violated the FDCA, the court ruled in favor of the defendants. In his opinion, Judge Harris wrote that the FDA was permitted to make exceptions when informed consent was deemed "not feasible" or "contrary to the best interests" of the soldiers because of the newly adopted Interim Rule (29, 27). Additionally, Judge Harris stated that FDA was not obligated define "not feasible" and that "not feasible" did not necessarily have to mean "impossible," as argued by Doe (29, 16). Judge Harris reiterated that the FDA's change from traditional feasibility was permitted for the combat situations and permissible unless the change was "manifestly contrary to the statute" (26).

Regarding the second claim that the DoD was violating 10 U.S.C. § 980, that consent was required "for any research involving a human being as experimental subject", Judge Harris sided with the defendants. The plaintiffs argued that the use of

INDs constituted “research”; Judge Harris disagreed and stated that the use of the INDs by the DoD did not involve any scientific investigation under controlled circumstances that “research” connotes (13). The DoD had deliberated alternative methods and had chosen the best alternative. Furthermore Harris reiterated that the primary purpose of the drug was therapeutic, not scientific (26).

On the final charge, that the waiver of consent deprived Doe of his Fifth Amendment rights to due process, the court, once more, sided with the defendant (27). The court found that concerns regarding the safety of the troops constituted “legitimate government interests that . . . counterbalance an individual’s interest in being free from experimental treatment without giving informed consent” (26, 27). The court found that the DoD had “legitimate government interests” in administration of the INDs to the troops during the Gulf War in order to prevent unnecessary harm that may be encountered (26). The Court came to the conclusion that the use of INDs by the DoD was allowed because “strategic military decisions” were at risk and dismissed all charges (26).

John Doe soon appealed the District Court’s decision. The Court of Appeals for the District of Columbia heard the appeal on March 18, 1991. At this time the war had ended and evidence was brought to prove that the military no longer needed to provide soldiers with pre-treatments (13). Since the war was finished, the Department of Justice argued that the case was moot and should therefore be dismissed (13). The Court of Appeals for the District of Columbia circuit, in a majority vote of 2-1, disagreed (27). Judge (now Justice) Ruth Bader Ginsberg wrote the majority opinion, in which she first addressed the issue of mootness and then analyzed and dismissed each of Doe’s claims.

Judge Ginsberg stated that even though the DoD no longer required the use of the drugs, the rule was still in effect and “capable of repetition” and, therefore, not moot (26, 27).

In its decision, the majority upheld the FDA’s authority to create Rule 23 (d) (the Interim Rule) stating that the term “non-feasible” was “well within the ordinary meaning’ of the words Congress used” (26). Additionally, Judge Ginsberg found that Congress’ intentions with its wording were vague, and the FDA interpretation was a “permissible construction of the statute” (26). In regard to the interpretation of feasibility, Judge Ginsberg noted that even though the prior conditions were based on the condition of the recipient of the drug, the addition of the Interim Rule to allow “impracticable [due to military circumstances]” to the non-feasibility of consent was permissible (27).

The court further agreed that 10 U.S.C. § 980 (Defense Appropriations Act), which prohibited the conducting of research without prior consent, was not violated by the passing of Rule 23(d) (13). In her ruling, Judge Ginsberg emphasized that the Defense Appropriations Act (DAA) restricted the authority of the DoD and not the authority of the FDA Commissioner (27). Therefore, Rule 23 (d) itself was not bound by the DAA. Though Judge Ginsberg did concede that “the DAA restricts the authority of the Assistant Secretary of Defense to make the request anticipated by Rule 23 (d), it cannot be argued that the DAA restricts the Secretary of Health and Human Services from promulgating Rule 23 (d)” (26).

On the final charge, Judge Ginsberg wrote that for the Fifth Amendment to invalidate Rule 23(d), Doe needed to show that no possible use of the Interim Rule could be reconciled with the Fifth Amendment (27). Judge Ginsberg concluded that the prevalent government interests in preventing harm and danger to troops outweighed the

interest of the individual in giving informed consent for the use of INDs (27). This claim supported the previous district court's ruling and agreed that the Interim Rule did not violate the Fifth Amendment's right to due process.

In the dissent, Judge (now Justice) Clarence Thomas argued that the case was moot and "now that the war has ended, Does' dispute with the defendants is purely hypothetical and their interest in the outcome, academic" (26). He further stated that Doe's situation did not fall into the "capable of repetition, yet evading review" exception to the mootness doctrine and that the majority was "focusing on the possibility of the rule reoccurring rather than the likelihood of Doe facing another application of the Interim Rule" (26). Judge Thomas stated that for the circumstances in which Rule 23(d) would have to be invoked, "is improbable alone and virtually unimaginable in sequence" (26). Judge Thomas also emphasized the fact that the likelihood of biological and chemical warfare will subside in the future and that the majority "surely overstate[d]" the risk of these attacks on soldiers, saying that "after all, American soldiers have not been victims of organized chemical attack since the First World War" (27, 26).

The fact that the majority of the court did want to comment on the case and yet, did not dismiss it emphasizes the important nature of this case. The waiving of informed consent had never previously been an issue that incurred much scrutiny and debate. After the passing of the Interim Rule, there were many arguments and articles that highlighted the controversy behind the rule.

### ***Brief Literature Review***

Scholarship regarding the issuance of the Interim Rule and the use of INDs in the Gulf War remains extremely polarized. Publications argue whether or not the soldiers should have been given the INDs and if so, should they have been given without consent. The issue of whether or not soldiers should have been given INDs is largely based on the safety of the drugs. The literature to be examined includes Ryan 1997, Annas and Grodin 1992, Boyce 2009, Howe and Martin 1991, and Levine 1991.

Commentary by Howe and Martin state that the INDs to be used by the DoD were considered to not be any “exotic new drugs” and had “well established uses” and therefore the INDs should have been considered safe to give soldiers (28). However, in response, Ryan (1997) makes it known that the safety was still in question. Ryan states that even though the planned usage by the DoD was only 15% of the original dosage of PB for the muscular nerve disease, the tests for safety did not include long term tests on a large heterogeneous population for the use of PB as a pretreatment for chemical warfare (29). The tests conducted by the DoD excluded women as subjects, men who smoked, and those that had abnormal blood pressure (29). The tests also studied immediate reactions to the drugs, not long-term effects of usage as pretreatment in a military environment (29). Some of the soldiers even had serious side effects including loss of conscious, vision problems and even respiratory arrest (29). This was all overlooked by the DoD in requesting for the waiver for the use of PB and was exposed later (30). Therefore, we can only be skeptical about what the DoD stated about the drug and the long history of its use and its safety. It is clear the DoD had its own agenda to fulfill and the safety and efficacy of PB must be reexamined.

Even if the drugs were safe, should the use of INDs have been considered research or treatment (terms used interchangeably with treatment include practice and therapy)? In addressing this issue, several articles, including Howe and Martin, allude to the Belmont Report, which states:

Although practice usually involves interventions designed solely to enhance the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(31)

The Belmont Report clarifies that just because there may be some elements of research and/or therapy does not warrant judging the act as purely one or the other because the lines can be blurred in some instances. Furthermore, before a procedure can be judged as research or therapy, the intent of the physician and the use of the drug must be examined (32). If the procedure is done in order to obtain systematic data for future use, then the intervention can be classified as research, but if the procedure is used primarily to help prevent further harm to soldiers than it can be considered therapy. This theory makes it seem that the use of INDs, at least in this particular instance, is legitimized as practice and not research.

Some scholars disagree. Annas and Grodin suggest that even if the intent of the physician is purely therapeutic it does not lessen the experimental nature of the drug (30). The fact that new usable knowledge will be generated from the use of the INDs during the Gulf War can also help categorize the use of INDs as research. Ethicists like Ryan

state that even when the intent was to use the drugs as a therapy, the fact that they were unproven and never used for the purpose of pretreatment before battle means it should have been categorized as research (29).

The biggest controversy in the current literature centers around the waiving of informed consent by the FDA and DoD under the grounds that consent was “not-feasible”. This literature (including Howe, Martin and Levine) contends that times of war are different and the restrictions placed on the use of INDs make them impractical. They argue that the use of investigational compounds should be allowed in combat situations to prevent unnecessary harm to servicepersons and that the obligation to protect military personnel overrides all other values, including that of informed consent (31, 35). Further, if the option of consent was given, many soldiers may have opted out of the INDs, thereby endangering the lives of their fellow service persons (28). The soldiers who did not take the INDs would have been the first to fall if Hussein’s army had used chemical and biological weapons. The soldiers who received pretreatment would have had to aid their fellow soldiers and this would hurt the overall military mission, negatively impacting morale and progress in the war (28).

In contrast, other ethicists (such as Annas and Grodin, and Ryan) hold the opposite view, arguing that informed consent is absolutely necessary and cannot be waived for the use of INDs. These ethicists state that military soldiers should be held in special consideration as a vulnerable population since the military has a history of conducting experiments without consent (29). Annas and Grodin further contend though it is in the best interest of the military to provide the best therapy available to troops in order to protect them, the military has no obligation to provide “experimental therapy”

(30). Instead, the military has an obligation to provide only “standard-of-care treatment”  
(30).

Since the US is still engaged in many conflicts overseas, threats of chemical and biological warfare may still arise. Therefore, I believe it is necessary to revisit this topic and explore it in depth. In the following chapters, I will examine the history and moral foundations of informed consent. I will then analyze whether or not the use of INDs during the Gulf War constituted an obligation of informed consent. Part of this analysis will be an examination of whether the use of INDs should be classified as research or therapy. This will be followed by an analysis of the ethical obligations fiduciaries have when they use unproven therapies and whether or not this too creates an obligation to obtain informed consent. I will then examine alternatives to the Interim Rule and conclude by discussing the shortcomings and current status of the Interim Rule.

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## CHAPTER TWO

### HISTORY AND SIGNIFICANCE OF INFORMED CONSENT

Informed consent is a pillar of American medical practice and research. This concept has allowed the transformation of the “doctor-knows-best” attitude to one that enables the patient to come to their own decision regarding their treatment and course of action. In this chapter, I first examine the moral foundations of informed consent and then provide an overview of the history of informed consent and how its presence as an ethical concept emerged.

#### ***Moral Foundations of Informed Consent***

The concept of informed consent arises from one of the basic principles of bioethics, respect for autonomy. The word autonomy takes root from ancient Greece, where *autos* means “self” and *nomos* means “rule” (1). Autonomy was first used in reference to political self-governance but has now come to mean personal self-governance in moral philosophy. Self-governance yielded the principle of respect for autonomy. This principle states that persons should be free to choose and act without control or constraints imposed by others. This principle provides the basis for persons to take their own course of action (1).

While this principle helps us construct the origin of informed consent, there is still no simple definition of informed consent. It encompasses so much that Beauchamp and Childress (2009) give two definitions of the term. First, they define it as “an individual’s *autonomous authorization* of a medical intervention or of participation in research” (1).

Their second definition alludes to the social rules of consent and states that “one must obtain legally or institutionally valid consent from patients or subjects before proceeding with diagnostic, therapeutic, or research procedures” (1). In obtaining informed consent, there are seven basic elements (A-G) that need to be fulfilled. Chief among these elements are the threshold elements, in which the subject has to be A) competent enough to be able to understand and make a decision for themselves (1). Along with this is the necessity that the subject is not being coerced and is B) voluntarily making a decision (1). These elements are followed by the important informational elements which include: C) full disclosure of information, D) recommendations for a course of action, and E) an understanding of the disclosure and recommendation (in order to make an informed decision) (1). This is followed by the consent elements which include a F) decision in favor of a plan and ultimately, G) authorization of a chosen plan (1).

These seven elements combined make up the process of informed consent. A subject must fulfill all these requirements in order to meet the standards of giving informed consent in a way that is respected and is fully autonomous. After examining the foundations of informed consent, I will now examine how informed consent emerged as a principle in the 20<sup>th</sup> century and its importance through its history.

### ***History of Informed Consent***

The concept of informed consent traces its roots back to the end of the World War II, when it was discovered that Nazi physicians were engaging in “biomedical experiments” upon authorization from their superiors. The physicians drew subjects from the populations of concentration camps (Jews, gypsies, Poles, and Russians), and

conducted “research” such as exploring the effects of ingesting poisons, intravenous injections of gasoline, immersion in ice water and even infection with jaundice and spotted fever viruses (2). The physicians were finally brought to trial in the 1940’s and a guilty verdict was given to all 23 defendants for crimes against humanity (2).

Upon the conclusion of the trial, the judges of the trial took upon the responsibility for establishing the “basic principles [that] must be observed in order to satisfy moral, ethical and legal concepts” in the conduct of human subject research (3). The list of these ten principles constituted the “Nuremberg Code”. The primary principle, Principle One of the Code, states that the “voluntary consent of the human subject is absolutely essential” and that persons involved should be “able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress. . .and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision” (4). The rest of the Code sets general boundaries as to how an investigator may conduct research and delineates the conditions under which a subject has the ability to volunteer.

Since the Nuremberg Code was formed mainly “by jurists for use in a legal trial”, the world medical community organized to develop a comprehensive set of professional ethical codes and guidelines that were more adequate for the needs for the research community (5). Therefore in 1954, the 8<sup>th</sup> General Assembly of the World Medical Association adopted its own principles in an attempt to regulate human experimentation (5). These principles became known as the Declaration of Helsinki. The Declaration’s fundamental principles are respect for the individual, the individual’s right to self-determination, and the right of the individual to make informed decisions regarding

participation in research (6). More importantly, the Declaration established guidelines stating that the investigator's duty is solely to "promote and safeguard the health of patients, including those who are involved in medical research" and that "the physician's knowledge and conscience are dedicated to the fulfillment of this duty" (6). The Declaration of Helsinki and the Nuremberg Code became the foundation for the development of international law and guidelines regarding biomedical research (7).

These rules and regulations, however, were not laws in the United States and therefore not strictly enforced and regulated. In 1974, Congress took on the responsibility of regulating research on human subjects with the passing of the National Research Act. Title II of the Act, the "Protection of Human Subjects of Biomedical and Behavioral Research," established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission). The Commission explored informed consent in various situations including consent among "special populations" such as children and prisoners (7). The Commission published its findings in 1979 as the "Belmont Report". This report set out the framework for national legislation regarding research in the United States, which was incorporated into codified law as Title 45 of Code of Federal Regulations Part 46 in 1981 (7). These rules became known collectively as the "Common Rule" when all federal agencies and departments (including the DoD) conducting research adopted them in 1991 to help guide and regulate research in the United States (7).

One of the most important requirements of the Common Rule was the need for an Institutional Review Board (IRB) to approve and ensure ethical standards for research. These IRBs could only approve the waiving of informed consent requirement if: "1)the

research involves no more than minimal risk to the subjects; 2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; 3) the research could not practicably be carried out without the waiver or alteration” (8).

By allowing an IRB to waive consent requirements the Common Rule took a different direction than the Nuremberg Code and the Declaration of Helsinki in regards to absolute respect for individual rights (7). It is also interesting to note that the Common Rule has special regulations for subjects of “special populations” such as children, prisoners, mentally challenged, and those who are pregnant. These persons receive special protections because of they may be at risk for coercion and may not know what they are agreeing to by participating in research. The military was not considered a “special population” and their rights were not specifically protected (7). Perhaps it should have been though, because during this time period the military had unique instances of not adhering to the requirement of informed consent in conducting their experiments.

One of these instances took place in 1955, when the Atomic Energy Commission conducted Operation Teapot, exposing four Air Force pilots to radiation clouds minutes after detonating nuclear weapons in order to determine how much radiation can penetrate the human system (9). Based on the results of the testing, military researchers concluded that the radiation encountered by the test pilots was the same inside the pilot’s system as it was outside (9). Though the Atomic Energy Commission limited the test pilots to fly into radiation of 3.9 roentgens or lower, the Air Force tests pilots flew were exposed to 15 roentgens putting them in a much greater danger than permissible by law (9, 10).

A year later, the Atomic Energy Commission conducted Operation Redwing, the continuation of Operation Teapot, and which authorized an increase of the test-exposure

limit to 25 roentgens (10). The supervisors, however, did not provide any additional protective clothing or increase the safeguards to help minimize the danger from exposure to the increased radiation. In 1995, General Ernest Pinson, one of the generals who supervised the studies, admitted to the President's Advisory Committee on Human Radiation Experiments that the experiments conducted by the Air Force did not provide any new scientific knowledge that had not been previously obtained from drone flights using mice earlier (9). Pinson further stated that he believed that conducting experiments such as testing the increase in radiation levels was thought to be part of the pilot's profession and not experimental; otherwise he "would have gotten written consent" before exposing the pilots to such significant levels of toxic radiation (9, 10).

At the time these operations were conducted, obtaining consent was not considered vital to conducting research, even though it was mandated at the time. The obligation to obtain informed consent was waived because participating in research was seen as part of being in the military. In Operation Teapot study, none of the pilots were told of the dangers of radiation. The pilots were expected to follow the orders of their superiors and were not given a chance to decline participation in the study (10). A second instance of military oversight in conducting research takes place in the 1960's.

In the mid 1960's, researchers in the US Army wanted to test the vulnerability of the subway system in New York City in case of chemical and biological attacks. In order to do this, the researchers dropped light bulbs that contained bacteria in to the ventilation system of the subway, exposing over a million people to the bacteria(9). The releasing of bacterial agents was conducted without the prior permission of the city or warning to the local population of any harms or dangers. Persons who rode the subway had no idea that

the air they were breathing had been exposed to bacteria or aerosolized agents such as zinc cadmium and that they could become seriously ill as a result (11).

Instances of abuse by the military compelled Congress to approve Title 10 of the United States Code (USC), Section 980 in 1972. This statute required that:

Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless:

- 1) The informed consent of the subject is obtained in advance; or
- 2) In the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance

(12)

This Code would serve as the primary document governing human experimentation for the DoD and required mandatory informed consent before any research is conducted.

These rules and principles help highlight the importance of obtaining informed consent particularly when research is being conducted and/or unproven therapies are being used.

During the Gulf War, soldiers were not given any say in the matter. The waiving of informed consent in December 1990 led the distribution of INDs to almost 700,000 soldiers and the FDA along the DoD put at stake this sacred principle of bioethics. In the next two chapters, I will demonstrate that the DoD had no other choice but to give the INDs forcibly to the soldiers in order to protect them.

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## CHAPTER THREE

### RESEARCH V. THERAPY AND THE WAIVING OF INFORMED CONSENT

Title 10 of the United States Code (U.S.C.), Section 980 states that “funds appropriated to the Department of Defense may not be used for research...unless the informed consent of the subject is obtained in advance” (1). Therefore, if the use of INDs constituted research, then the DoD would have been required to obtain informed consent and should not have gotten the waiver for informed consent. In this chapter, I will discuss why the use of INDs constituted therapy rather than research, making it permissible for the DoD to administer INDs without consent. In order to do so, I will first examine what constitutes research versus therapy. I will then examine why the use of INDs is considered treatment and why there was no obligation for the DoD to obtain informed consent from the soldiers treated with INDs.

#### ***Origins of the Debate Between Research and Therapy***

During the 1960's and 1970's, the American public was exposed to the horrors of medical research, which led to the creation of specific rules regarding human biomedical experimentation. The first revelation that rocked the American landscape was an article written by Henry K. Beecher that was published in 1966 in the *New England Journal of Medicine*. His article, “The Ethics of Clinical Research” drew attention to over fifty cases, though he only selected 22 for publication “for space” (2). Beecher's article provided detailed cases of serious or potentially serious ethical violations that had occurred in research, including violations of informed consent. Some of these

experiments had a high ratio of risk to benefit and involved vulnerable or disadvantaged subjects who were unaware of their participation in the research (2). These individuals were essentially taken advantage of under the guise of treatment. In one of the experiments, physicians substituted placebos for an established effective treatment for respiratory infections (2). The physicians had no reason to give placebos, but did so in order to provide data on the effectiveness of the drug given. In another case, physicians administered chloramphenicol on patients, which is known to induce potentially fatal aplastic anemia, without their knowledge (2). Of the 403 patients treated for typhoid with chloramphenicol, 23 patients died needlessly for the sake of the “study” (2). This article sparked outrage in America about the unethical practices of research and medicine. However, this was only the beginning of exposure of unethical practices in the United States.

A second more serious case was uncovered in July of 1972 by the *New York Times*. The case, known as the Tuskegee Syphilis Study, involved the U.S. Public Health Service who denied treatment to almost 400 black men with syphilis in a forty-year experiment (3). This study began in 1932 and continued until 1972 when it was halted due to public outrage (3). The purpose of the study was to examine the long term effects of syphilis on 400 poor African American males who all had syphilis but were unaware of it. The participants were told that in exchange for taking part in the study they would be given free medical exams, free meals and free medical insurance (3). The men who enrolled in the Tuskegee Syphilis Study were never treated for syphilis, even when penicillin was found to be an effective cure in the 1950’s. Instead, they were observed in order to see the long-term effects of syphilis. The researchers even prevented other

doctors from treating the men with syphilis and it is estimated that as many 100 men died as a result from being untreated for almost 20 years after a cure was found (3). The truth about the study was finally publicized in 1972 by a researcher who had worked on the project. These scandals prompted Congress to take action and on July 12, 1974, Congress passed the National Research Act.

This Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission). The main objectives of the Commission included conducting “a comprehensive investigation...to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects” (4). Congress further asked the Commission to examine “the boundaries between. . . research involving human subjects and the accepted and routine practice of medicine” (4). Therefore, Congress wanted the Commission to examine the philosophical “boundary problem” and sought to define at what point “research” becomes accepted medical “practice” (4).

The Commission published its findings on April 18, 1979 in a report titled the Belmont Report. The Belmont Report sought to create a framework for ethical human biomedical research, which included definitions of what constitutes research and what constitutes therapy. The Belmont Report defined research as “an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge...” In contrast, practice is defined as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success” (4). The Belmont Report goes on to state that the only time that research and practice can be carried out together is when “research is

designed to evaluate the safety and efficacy of a therapy.” In coming up with these definitions, the Commission looked at two very important factors: first, the level of risk and second, the intent of the physician.

### ***The Level of Risk***

One of the biggest distinctions between “research” and “practice” is the amount of risk encountered. Research, by its very meaning contains process or drugs which are new and whose effects are not fully known (5). The newness and uncertainty involved with research means that the level of risk will be much greater, and if unnecessarily applied to a human subject, such a procedure could lead to injury and harm stemming from limited knowledge (6). In contrast, practice refers to therapies and procedures that are usually standard practice and are meant to be purely therapeutic in nature (6). Contributors to the Belmont Report alluded to the FDA drug approval process to help illustrate the spectrum between the level of risk and research and practice.

The drug approval process generally consists of three periods known as Phases I, II, and III. Phase I involves initial testing of the drug. This phase determines whether or not the drug is safe for human use (6). In order to gather data regarding the safety of the medication, subjects receive the drug and are closely monitored (6). This phase is highly risky as there most likely is no prior data regarding the use of the medication in humans (6). For these reasons, this phase is limited to about 20-80 subjects (6). Once this safety is demonstrated, testing proceeds to Phase II

The degree of risk to humans is somewhat decreased in Phase II of the drug approval process. In this phase, investigators shift their focus from determining the safety

of the drug to evaluating the efficacy of the drug for its intended purpose (6). Since the side effects of the drug are still largely unknown, testing of the drug is still limited to only 100 to 200 subjects (6). These subjects are monitored, usually weekly, to ensure that the drug is safe and effective (6). After the safety and efficacy of the drug has been demonstrated, the drug moves to Phase III testing.

In Phase III testing, a much larger population is exposed to the drug. The population size increases from a couple hundred to several thousand subjects (6). This allows investigators to fully identify the drug's interaction with a large range of subjects and to document evidence of safety and efficacy. It is important to note that at this point the drug is still classified as "investigational" and still has not been approved for use by the FDA (6). By the end of Phase III trials, there is well-established evidence of the drug's safety and efficacy, and doctors may start prescribing it for a specific condition (6). However, due to FDA regulations, it may still be years before the drug is formally approved. By the end of Phase III, the drug is recognized for a specific purpose and is prescribed by doctors and the use of the drug no longer constitutes research. This whole process from start to finish can take 10 to 20 years (6).

This FDA approval process illustrates the spectrum of "research" to "practice" use of drugs. Research generally involves high risk and medical uncertainty, while practice is concerned with treating the ailment and not with the acquisition of knowledge. The acquisition of knowledge regarding safety and efficacy that is developed in Phase I leads to effective practice and therapy by Phase III. The level of risk decrease as the phases progress. This decreasing level of risk from the new drugs is just one of the

criteria to help assess whether a procedure is research or therapy; the other is the intent of the physician.

### ***Intent of the Physician***

The Commission made an important distinction between research and therapy when they stressed the significance of the physician's intent. One of the writers of the Belmont Report stated that physicians engage in "therapy" when they seek to benefit only the patient through the best-known treatment, while a physician engages in "research" when new knowledge is developed through the dealings with the patient (7). The physician's intent is important because it helps to determine whether there is a conflict of interest between the physician and the patient. This is because it can help provide evidence whether the procedures are being carried out in the patient's best interest or to the boost the scientific and career goals of the physician.

The problem arises when the procedure being carried out contains mixtures of both research and therapy. In order to help determine whether the activity should be considered research or therapy, Robertson suggests looking at the "primary intent" of the physician (7). If the physician's primary intent is to obtain new knowledge regarding the disease, then it is research. For example, if the primary use of the drug is not to treat the patient, but to test the effectiveness, then it can be considered research and not therapy. In contrast if the primary purpose of the drug is to treat the patient and not collect data, then the procedure can be considered therapy. Using the criteria established by the Belmont Report, I will now examine whether or not the use of INDs by the DoD is considered research or therapy.

### ***INDs: Research or Therapy?***

When the DoD applied for a waiver of informed consent, both PB and the botulism vaccine were classified as investigational new drugs. As such, PB was licensed by the FDA as safe and effective for the treatment of myasthenia gravis and the side effects of anesthesia and was in the “investigational” stage for use as a pretreatment in military combat. The other drug, botulism vaccine, was a vaccine used to immunize at-risk persons but had never been approved for the DoD military purpose and was too labeled as “investigational”. Neither drug had ever been used in large populations in a military combat environment nor were they ever approved for such a purpose. The FDA passed the Interim Rule in late 1990 allowing for the waiver of consent for the use of INDs by the DoD. In its appeal to the FDA, the DoD stated that the INDs were being used strictly as therapies and that informed consent was not feasible. However, there were many critics including Annas and Grodin, and Caplan who disagreed and said that the use of INDs constituted research.

Critics of the Interim Rule immediately argued that use of INDs constitutes research because of the “manifestly experimental” nature of the investigational drugs (8). However, in response, the label “manifestly experimental” comes from misunderstanding the word “investigational” in investigational new drug. Just because the drug is labeled as investigational does not mean that it cannot be therapeutic in nature and that its purpose is primarily for research. As we can recall from the FDA drug approval process, a drug that is still considered “investigational” can be widely prescribed by doctors for treatment purposes.

The same critics argue that since the drugs “were used in large populations for purposes other than those for which they were originally designed in circumstances under which they had never been tried before,” they should be considered research (8). This too is a weak argument when the use of INDs is examined through the two factors in the Belmont Report, the level of risk involved, and the intent of physician.

The level of risk can help determine whether or not a procedure should be considered research or therapy. Those procedures that are considered research generally constitute a higher level of risk than those that have come to be accepted as common practice. The use of INDs can constitute research because the level of risk (harm from the use of INDs) is higher than no pre-treatment at all since the use of INDs may have adverse effects on the soldiers. In contrast though, if the DoD had given no pre-treatment, the level of risk faced by soldiers in battle would be much greater if they faced chemical and biological weapons.

In asking for the waiver the DoD had conducted its own research to provide enough evidence to its IRBs and the FDA that the use of INDs was safe and effective with a minimum the level of risk. This leads us to the second factor in the Belmont Report to help determine whether a procedure is research or therapy—the intent of the physician.

The intent of the physician also helps to determine whether a procedure should be considered research or therapy. The Belmont Report states that the “purpose of medical or behavioral practice is to provide diagnosis, preventative treatment or therapy to particular individuals [or groups of individuals],” while research occurs when the aim is primarily to “test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge” (4). Thus, the intent of the physician plays a big

role in helping to determine whether or not a drug or procedure can be considered research or therapy. In the case of the INDs used, the intent of the DoD was to provide preventative pretreatment to protect the soldiers from harm that may come from chemical and biological weapons in the course of war. This allows us to determine that the use of INDs should be considered therapeutic and not research.

Ethicist Arthur Caplan, however, argues the intent of the physician is too subjective of a determinant. He states if the physician's intent was the determining factor, "those who do research would merely have to change their intentions and they could succeed in making the most innovative and experimental medical interventions into therapies merely by a change of mind" (8). Other critics argue that it should not be the intent of the physician that determines whether or not a procedure or a drug is considered investigational, but rather the "nature of the intervention...that determines whether or not an intervention is research or therapy" (9). In this case, Annas and Grodin argue that the INDs were used for research purposes.

However, the nature of the intervention was as therapeutic as possible and was not done for investigational purposes. The DoD did all the testing that it could have in order to prove safety and efficacy of the INDs in the limited time they had to get the drugs approved before deployment. The only other way that the DoD could have proven the drug's safety and efficacy was to expose actual human test subjects to the chemical and biological weapons. The use of INDs in such a setting will always be "experimental" since you cannot ethically test the drugs on humans, but it should be considered therapy because of the nature and purpose of the intervention (10). In the following passage, Hans

Jonas explains that, in the doctor-patient relationship, the nature of the intervention is most important:

As long as a doctor can say, even if only in his own thought: “There is no known cure for your condition (or: you have responded to none); but there is promise in a new treatment still under investigation, not quite tested yet as to effectiveness and safety; you will be taking a chance, but all things considered, I judge it in your best interest to let me try it on you”—as long as he can speak thus, he speaks as the patient’s physician and may err, but does not transform the patient in to a subject of experimentation.

(11, 10)

Since in this context there was 1) no *preventive* treatment available at the time in case chemical and biological weapons were encountered and 2) the DoD was using INDs for a purely therapeutic purpose in preventing any harm that may befall the troops, the use of INDs during the Gulf War should be considered therapy and not research. If the use of INDs was considered research, there would be a need to obtain informed consent from all the troops. However, in the military, consent is not required for the administration of therapies.

### ***Consent for therapy***

Persons who join the military give up some of their autonomy. This is because military personnel must obey their commanding officer and abide by the rules and customs of the military (14). One autonomous choice that service members give up is the right to provide consent for therapy. Military physicians, through their commissioning and oath of office, are authorized by the Secretary of the Army to do whatever it takes (as necessary) to make soldiers fit for duty (12, 13). Military physicians are usually the ranking officers in treating the soldiers and the soldiers have sworn an oath to obey the lawful orders of those above him or her (14). By not having an option of consent the

military can ensure that soldiers will be healed and be able to fulfill their obligation towards the military in accomplishing its goals. The military needs the soldiers to be healthy; therefore it has to provide treatment in order to make them able to perform the tasks required.

In the past, military commanders have determined that the need for soldiers is so great that they may require ill and/or injured soldiers to return without proper treatment. For example, in 1942, during the battle for Guadalcanal in the Pacific, up to 90% of the soldiers were infected with malaria (6). If all those infected received treatment, the ranks of the troops would have crumbled and the US would have lost the battle (15). Recognizing such a dilemma, General Alexander Vandergrift who was in command of the 1<sup>st</sup> Marine Division, ordered doctors “not to excuse soldiers with a temperature of 103 or less” (15, 5). This decision was made so soldiers could hold their lines and the 1st Marine Division would not lose the battle due to the malaria epidemic.

In the case of the INDs used in the Gulf War, the soldiers were given the INDs as therapy in order to ensure that they would be fit for combat and not be lethally affected by the use chemical and biological weapons by the Iraqi Army. The DoD was well within its bounds to administer them without consent.

There were doubts regarding the safety of the INDs that led to their being labeled as unproven therapies. Ethically speaking, the use of unproven INDs without informed consent still violates the rights of soldiers. In the next chapter, I will examine why even though the therapy was unproven, the DoD did not have an obligation to obtain informed consent prior to administering the INDs.

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## CHAPTER FOUR

### UNPROVEN THERAPIES AND THE WAIVING OF INFORMED CONSENT

Sergeant Carol Picou was a US Army nurse who experienced first-hand the effects of PB during Operation Desert. Picou was ordered by her field commander to take PB every eight hours throughout the day (1). Soon after starting her daily dose, Picou began encountering some of the side effects of PB (1). Picou's "eyes became blurry; she drooled; [and] she lost control of her bladder" (1). In order to counter the effects she skipped a dosage of the pill, but her superior officer refused to allow that to happen (1). He even watched to make sure she didn't skip her pill. "This is for your own protection. You need to continue...taking this as long as we're in Iraq," she remembered him saying (1). Today, Picou's condition has worsened. She suffers from severe incontinence that requires her to "wear diapers and catheterize herself eight times a day" effectively ruining her life (1). Furthermore, in 1992, Picou was diagnosed with a disease that effects her immune system which she believes was caused by PB (1).

Sgt. Picou's suffering demonstrates that the unapproved use of drugs can be extremely detrimental to a person's health. In this chapter, I will look at the questions regarding the safety of PB and its administration as an unproven therapy. After this, I will examine the informed consent requirement that is created from the use of INDs as unproven therapies, and why the DoD was still obligated to waive informed consent and require the use of INDs without consent.

### ***Safety and Efficacy of INDs***

Before military testing, PB had been approved by the FDA as a treatment for myasthenia gravis, a neuromuscular disease, with few adverse reactions (2, 3). The use of PB to treat myasthenia gravis had been documented since 1955 at doses even six times greater than that proposed by the Department of Defense (3, 1). FDA officials stated that because of the long-term use of PB in the treatment of myasthenia gravis, they were satisfied with the safety of the drug (1). However, when we delve further into the use of INDs, especially PB, we will see that the data regarding safety and efficacy was lacking.

Historical documentation of the safety and efficacy of PB was based solely in a clinical setting for the treatment of myasthenia gravis. When the DoD applied for the waiver of consent to treat military personnel with PB, they had been stockpiling PB since 1986 (4). This implies that the military foresaw the eventual use of PB in combat. Even though they had been stockpiling the drug for at least five years before use, there was no effort made by the DoD to collect basic safety data on PB until right before the threat of war with Hussein (3). The DoD had also failed to include in their negotiations with the FDA a then-ongoing study conducted by the Army that was evaluating the effectiveness of PB as a pretreatment for biological and chemical weapons (4).

This study was conducted by the US Army Medical Research Institute of Chemical at the Aberdeen Proving Ground in Maryland. The study showed that when rodents were exposed to different chemical weapons (other than soman) such as sarin or VX, the effects of the treatments for these common nerve gases were negated by the presence of PB (4). This is alarming since PB is prescribed as a pre-treatment for soman only and Saddam Hussein was known to possess sarin and VX in addition to soman (5,

1). The DoD is required to update the FDA with any new information about the drugs for which it sought waivers (4). The Army study that demonstrated PB's ability to negate the effects of other chemical agents was ready for publication on February 11, 1991 and was completed in early 1990—this was before the DoD applied for waiver (6). The DoD, however, claims that it was unaware of the Army study because it was conducted by a different research group of the Army and was unrelated to the application for the waiver (1). This lack of communication between the different groups allowed the DoD to submit the application for a waiver without citing this important study.

The research conducted by the DoD also stopped just short of endorsing long-term use of PB as a pretreatment on a large-scale heterogeneous population (1). Almost all of the studies that tested PB were exclusively on males and excluded women as subjects even though women serve as soldiers in the army (7, 1). A doctor indicated on a staff senate committee that there are differences in physiologic responses to PB in different genders, including incontinence and diarrhea in females (7). It turns out that DoD studies also excluded men who smoked, took medication, or had abnormal blood pressure (7, 1). Such a study is not reflective of the overall population of the army and demonstrates the DoD's lack of care and responsibility in thoroughly evaluating the safety of PB in military personnel. Some critics have gone so far as to point out that the studies involved a smaller number of subjects and sought to ensure that there were no reasons for the drugs to be rejected (1). Furthermore, the research conducted by the DoD focused just on the immediate reactions to PB and did not include follow-up assessments of potential long-term effects (7). It also seems that the DoD arbitrarily limited the use of PB by military personnel to twenty-one days in order to minimize any unknown long-

term effects (1). Of the subjects tested, some suffered serious side effects upon ingesting PB, which included fainting, problems with eyesight, and abnormal liver tests (7, 1). In fact, one Army pilot even went into respiratory arrest after his third dose of PB (7, 1).

When researchers examined PB's interaction with other chemicals that would be used in combat, the safety of administering PB to military personnel was cast into further doubt. It is common procedure in the military to spray the combat area with insecticides in order to prevent harm from coming to troops (1). A study conducted by the Duke University Medical Center provided evidence that when these insecticides were used in conjunction with PB complications could arise from potential interactions that included serious skin damage (1). These side effects ranged from total paralysis to death. Another study by the University of Texas Southwestern Medical Center showed that people who have taken PB with pesticides can suffer subtle nerve damage, potentially resulting in "fatigue, dizziness, disorientation, and muscle weakness" (1, 8). Ultimately, a study conducted by Dr. James Moss at the Department of Agriculture found that when cockroaches were administered PB and exposed to a common insect repellent, diethyl-m-tolamide (DEET), the DEET became "almost seven times more toxic and PB became four times more toxic" (7).

The animal studies conducted by DoD were also lacking in providing adequate evidence of efficacy. In the studies conducted by the DoD, even with PB pre-treatment, monkeys exposed to soman still rapidly developed paralytic seizures (3). These uncontrolled seizures began as early as twenty-four hours after exposure and led to brain lesions similar to those of monkeys who did not receive PB pretreatment and died (9). Therefore, even if the use of PB helped prevent initial damage from soman, exposed

subjects were still likely to develop brain seizures that lead to paralysis akin to those who did not receive pretreatments. One of the only studies involving the accidental exposure of humans to nerve agents provides evidence of the lack of efficacy.

When humans were accidentally exposed to nerve agents, long-term behavior changes and brain lesions were found (10). The study suggested that there would have been a similar effect even if those accidentally exposed were pretreated with drugs such as PB (10). These examples show that even if PB reduces the mortality rate of those exposed to soman, it does not prevent the potential for neurological damage. Therefore, even if the soldiers did not immediately die after exposure to nerve agents, there was still a chance of death due to secondary neurological damage from exposure to soman which PB is unable to completely prevent (9).

Questions regarding the safety of the drug were not just limited to the use of PB, but also the use of the botulism vaccine. The botulism vaccine was intended to protect against botulism, a disease wherein the bacterium *Clostridium botulism*, which naturally occurs in the soil, gets into the body via ingestion (1). The bacteria then produce a potent toxin that leads to respiratory distress and eventual death if left untreated (11). What is disconcerting about the vaccine is that the supply given to soldiers by the army was more than twenty years old and the army had no concerns the vaccines could have broken down into toxic products (4). One FDA reviewer pointed out during the Informed Consent Waiver meetings that the Centers for Disease Control considered terminating the vaccine because of the number of persons who had encountered the side effects of the drug (4). The vaccine only protects against two of the of the five different strains of

botulism and the manufacturer of the vaccine reported that there had not been any studies carried out on the vaccine's effect on pregnant women (4).

Furthermore, the botulism vaccine was administered to recipients at the onset of the war and in order to be effective it was supposed to be given in a series of four injections. The first was at week 0, the second at week 2, the third at week 12, and then the last injection at the end of 12 months (1). However, because the war lasted barely over a month, most soldiers were given only two doses of the vaccine (12). This means that many of soldiers did not receive their last two booster shots and could end up harming them and negating the intended effects of the botulism vaccine because of improper dosage (4, 12).

In asking for a waiver of consent, it seems as if the DoD selectively provided information to the FDA regarding the safety of the drug in order to ensure that it would receive the waiver of consent. The questions regarding the safety and efficacy of the INDs help us classify them as unproven therapies, therapies that may work for their intended purpose but may still carry a significant level of risk. The use of unproven therapies usually creates an obligation to obtain informed consent.

### ***Unproven Therapies***

In the civilian world, the use of unproven therapies would almost always require consent from the patient because the therapy is outside the realm of standard accepted treatments and may carry a greater amount risk. Even though the administration of therapies that make soldiers fit for duty can be performed without consent, there is still an

interesting instance in the military where the use of unproven therapies is prohibited and may entail a consent requirement.

This instance comes from a court hearing in 1953, in which the accused soldier was to be court-martialed for refusing to a surgical operation known as vesiculotomy (13). This procedure, though first used many years ago, was shown in the trial to not be a universally accepted treatment by the medical profession. In his final ruling, the Judge Advocate General held that the victim could not be court marshaled because “as far as major operations are concerned, only those so thoroughly tried and generally used by the medical profession that they have definitely and finally passed the novel and experimental stages and have been accepted as standard operations” can be performed without consent (13). The court further ruled, “not only must this requirement be clearly met, but it must also be shown that such an operation is generally recognized by the profession as being a cure for the particular diseases with which the subject of the operation is afflicted” (13).

This ruling states that only those procedures that are thoroughly tested, have passed the novel stages, and are considered standard-of-care should be performed on soldiers. However, the 1953 ruling does not take into consideration what would occur if the unproven therapy were the only treatment available and there were no proven standards of treatment available. This case raises an interesting consideration for the use of INDs: would the military have been liable for the soldier’s death following exposure to chemical and/or biological weapons if he or she did not consent to receive the available INDs as pretreatment? A subject undergoing a surgical procedure is very different from a subject taking INDs as a pre-treatment. In surgery, the subject is already unhealthy and

needs to be given the appropriate level of care in order to ensure proper recovery. In other words, the surgical patient is accepting risk to reap the benefits of a treatment for an existing condition. This is in contrast to the soldier receiving INDs as a pretreatment because the soldier is assuming the risks of the IND without knowing that he or she will actually reap the benefits of it (i.e. without knowing whether or not they will, in fact, come into contact with chemical and biological weapons.) Poignantly, there was no available accepted pre-treatment for chemical or biological weapons encountered in battle; only post-exposure antidotes were available. The INDs were given only to protect the troops and amplify their level of security in case of chemical and biological weapons. The unavailability of any other pretreatments renders the INDs the best possible option for protecting the troops. Even though the INDs have an investigational status, the DoD still would have given them regardless of the ruling because of the relationship between the soldier and the military.

The court-martial case, however, was the only case regarding standard-of-care practice in the military. Since the use of unproven therapies usually requires informed consent, I will now examine the ethical reasons why the DoD was still obligated to provide and administer the INDs.

### ***Ethics of Waiving Informed Consent***

When the DoD waived the rights to informed consent for the soldiers, they were violating the soldiers' autonomy. A person's autonomy has come to be defined as an individual's freedom to act independently, free from outside controlling influences (14). Beauchamp and Childress state that the philosopher, Immanuel Kant argued that:

“Respect for autonomy flows from the recognition that all persons have unconditional worth, each having the capacity to determine his or her own moral destiny. To violate a person’s autonomy is to treat that person merely as a means’ that is, in accordance with others’ goals without regard to that person’s own goals”

(14).

Based on Kant’s theory, the DoD and FDA were using the soldiers as a means to accomplish their mission by waiving their informed consent. However, Kant’s theory is not applicable in this case.

The military waived the requirement of informed consent in order to protect the soldiers from chemical and biological weapons. The military was compelled to waive the requirements through the principle of beneficence and its obligatory relationship with the soldiers. The principle of beneficence “refers to a statement of moral *obligation* to act for the benefit of others” (14). This principle contains some specific rules and obligations which include: 1) preventing harm from occurring to others and 2) removing conditions that will cause harm to others (14).

When a soldier joins the military, they enter a reciprocal relationship in which they obey and help accomplish the military’s goals in exchange for the military ensuring the soldier’s welfare and preventing harm to him or her. This reciprocal relationship is best described as a paternalistic one in which the military can intentionally override the soldier’s preferences, justifying this action “by appeal to the goal of benefiting or of preventing or mitigating harm to the person whose preferences or action are overridden (14).” The paternalistic nature of this relationship allows for the waiving of consent for the benefit of the soldier in order to protect them from chemical and biological weapons.

John Stuart Mill’s harm principle also helps justify actions taken for the benefit of others. The harm principle, which Mill includes in his book, *On Liberty*, states that the “only purpose for which power can be rightfully exercised over any member of a

civilized community, against his will, is to prevent harm to others” (15). Viewing the military’s obligation to its soldiers through Mill’s Harm Principle, it seems the military may legitimately limit the autonomy of soldiers in order to protect them. The paternalism of the harm principle is evident in the code of conduct in the military. For example, while in the civilian world “an accountant is free to be fat, because he alone suffers any ill effects; an infantryman violates another’s liberty by being grossly overweight. He harms those who legitimately depend on him to perform his job well” (16). Therefore, soldiers may not be permitted to be in less than peak physical condition since their ability to carry out a mission and lessen the risks to fellow service members depends on it. This correlates to the use of INDs. If a soldier were to deny the INDs, he would put at risk all his fellow soldiers.

In a military setting, it is evident that the principles of preventing unnecessary harm to others and accomplishing the mission override all other values, including the right to self-determination. The FDA’s waiver of informed consent for the use of INDs by the DoD falls well within the limits of the harm principle. If INDs were not given to the soldiers, many may have been incapacitated and died if chemical and biological weapons were used by the Iraqi military. This could have led to decimating ranks in battle, loss of war, and perhaps even more loss of life. Furthermore, if the soldiers were allowed to consent to the use of INDs, it is possible that many of them would have declined and this would put some soldiers at greater risk than others.

The fact that INDs were used as pretreatments to prevent further harm to soldiers has some grounds for justification through a very famous public health case (17). In the case of *Jacobson v. Commonwealth of Massachusetts*, the plaintiff, Jacobson, refused to

comply with a Massachusetts law requiring mandatory small pox vaccination. The case was heard at the Supreme Court in which it was held that Jacobson had to comply with the mandatory vaccine (18). In his opinion, Justice Harlan stated:

Society based on the rule that each one is a law unto himself would soon be confronted with disorder and anarchy. Real liberty for all could not exist under the operation of a principle which recognizes the right of each individual person to use his own, whether in respect of his person or his property, regardless of the injury that may be done to others. . . . [Thus,] in every well-ordered society charged with the duty of conserving the safety of its members, the rights of the individual in respect of his liberty may at times, under the pressure of great dangers, be subjected to such restraint, to be enforced by reasonable regulations, as the safety of the general public may demand.

(17, 18)

*Jacobson*. shows that it is permissible to restrain a person's individual liberty if the exercise of that person's liberty has a detrimental effect on others. In the military, refusing the INDs would have meant harm would be more likely to befall the soldier and his platoon if the chemical and biological weapons were used. The military ultimately had no choice and did all it could have done to protect the troops.

However, by administering INDs without consent, the DoD and FDA may have violated the bioethical principle of nonmaleficence. This principle states, "above all [or first] do no harm" (14). This principle is often proclaimed the fundamental principle in the Hippocratic tradition of medicine and ensures that health professionals act in the best interests of their patients and do not inflict evil or harm upon them (14).

In this case, since the safety of PB was in serious doubt, it is questionable whether or not PB should have been administered. The administration of PB may have caused more harm than good. After the troops returned from the Gulf, the Gulf War Syndrome plagued many of them. This illness is a multi-symptom, chronic disease that effects the livelihood of all those affected. In an investigation conducted by the Research Advisory

Committee on Gulf War Veterans' Illnesses, it was found that the use of PB in part contributed to the illness of these soldiers (19). The unproven nature of INDs should have made the DoD more cautious in the compulsory administration of the INDs.

Though the lack of evidence of safety and efficacy of the INDs did create controversy, it is clear that the military had to administer them to the troops without consent. The DoD had a duty to protect and safeguard the troops; this obligation overrides the obligation to obtain consent. In its reasoning, the DoD emphasized that the soldiers would have been endangered if the INDs were withheld. If soldiers were given the option of consent, many of them could decline the use of INDs. If this had occurred, the soldiers would then become a liability, be in even more danger, and hurt the mission. In order to protect them from harm to themselves and others, legal regulations of the military along with the harm principle allow the administration of therapies without consent.

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## CHAPTER FIVE

### ALTERNATIVES

The Interim Rule (the Rule) was passed on December 21, 1990. The Rule allowed the commissioner of the FDA to determine whether or not obtaining informed consent was feasible in certain combat situations. It permitted the commissioner to consider a waiver for a single military request by the DoD “involving combat or the immediate threat of combat” (1). This Rule was implemented in the Gulf War and allowed the distribution of PB to almost 700,000 soldiers and the botulism vaccine to about 8,000 people (2).

The Rule worked as intended and allowed the use of INDs without consent. However, the Interim Rule also violated a major principle of bioethics, the soldiers’ right to informed consent, thereby raising questions regarding the rights of military personnel. In this chapter, I will examine some alternatives to the Interim Rule that have been suggested and see which alternative best protects the soldiers’ right to informed consent and still help achieve the objectives of the military.

#### ***Revocation of the Rule***

The first alternative (as suggested by Rettig, 1999 and Ryan, 1997) to the Interim Rule is to revoke it and have no rule at all. However ideal this sounds, it would, would be impossible in our current day and age to do. The US is currently engaging in more and more international conflicts, where there is still a very real threat of biological and chemical weapons. If the Rule is removed it would take away the military’s ability to use

any INDs that may help save the lives of soldiers. This is something neither the FDA nor the DoD desire. As it stands, the Interim Rule has some protections in it which included an IRB review for the required protocol, adjudication by the FDA commissioner, and the assurance that no alternative treatments or therapies were available. This still does not completely respect the autonomy of the soldiers being given the INDs.

Therefore, the rule itself should not be revoked but amended to provide greater protections for soldiers' autonomy. This leads to the second alternative to the current Interim Rule, the creation of a new "military use" category of drugs.

### ***Military Use Category***

A second option looked into by the FDA was the creation of a new category for military drugs to be used by the military (2). This new category would be limited to drugs that are to be used exclusively by the military in the military exigencies such as those exhibited during the Gulf War. The category would require a thorough process to test the safety and efficacy of the drugs to ensure the utmost care is taken for the benefit of the soldiers. This kind of category would be ideal for the military because it would allow them to take unapproved drugs that may be beneficial to them in circumstances of combat.

However, there are many questions that need to be addressed in order to create such a category. For example, who would be in charge of judging and classifying what drugs should go in the special military category and how the safety and efficacy is measured? Questions regarding the process of testing also are important. Should the testing and approval process be the same as those used in commercial drugs, or should it

have a higher standard? Would animal testing suffice; what would qualify as satisfactory data in the approval process?

In my opinion, the creation of a new category would be too complicated and complex of an undertaking. There are too many issues regarding the classification of drugs, the testing for safety and efficacy, and the administration of the drugs for this to be a viable option. In theory, the creation of a new category could work, but this new category would also be vulnerable to abuse. For example, the military may pressure the governing body of the special category to include drugs that have not yet been demonstrated safe and effective for use. A military use category for drugs could end up harming the soldiers instead of helping them. A third and final alternative to the Interim Rule and one that may help balance the interests of the military with the interests of the soldiers is anticipatory consent.

### *Anticipatory Consent*

The option of anticipatory consent was proposed by the FDA in its Request for Comments in 1997 and further discussed by Retting (1999) (3). It is a concept in which consent is obtained from the subject before the anticipated need. For example, consent for the anticipated use of INDs would have been obtained before the soldiers' deployment to the Gulf. In looking at anticipatory consent as an alternative we will examine its viability from three potential points in a soldier's career (2). The first point is before recruitment, the second before starting basic military training, and the third point in which anticipatory consent may be obtained would be before deployment (2). The potential of each time period will be examined using this criteria: 1) the ability to obtain consent at that time, 2) the

range of INDs to be used, 3) the duration of the consent to be had, and 4) the consequences of refusal of informed consent (2).

The timing of the consent is important because it is what differentiates informed consent at the time of use with anticipatory consent obtained in advance (2). If anticipatory consent is obtained too far in advance, the individual may not consider the gravity of what he or she is agreeing to and the impact in future missions where it will be invoked. Likewise, if informed consent is obtained right before administration of a drug, the benefits and risks of the drug may receive exaggerated attention.

Intertwined with the timing of the consent is the content of the information that will be provided during the obtaining of anticipatory consent (2). The information that the officers provide to the soldiers could be critical in obtaining consent. Do the officers disclose all risks or just lethal ones? Should the officers describe the potential for use by the enemy? The amount of information provided could impact a soldier's decision to accept or decline the benefits and risks of the medication.

Additionally, the scope of consent is important (2). Will the anticipatory consent cover all drugs or just the ones that meet certain criteria? The scope will also examine whether or not experimental medical procedures and experimental devices should be included, or just experimental drugs. Also, would the scope of consent be different for products that are administered by a medical professional as opposed to "self-administered" (2)?

The scope of consent leads us directly to the question regarding the duration of consent. If anticipatory consent is given, for how long should it be valid (2)? Should it be valid for the duration of the conflict; or for some other arbitrary amount of time, such as

twelve months? Consideration of the duration of anticipatory consent is very important because it will help determine whether or not soldiers have provided consent to take a particular IND for a particular military mission (2).

Ultimately, the biggest concern with anticipatory consent is the same reason why the Interim Rule was passed in the first place: what if consent is declined (2)? In the civilian world, refusal to consent would not carry any non-medical consequences (2). However, in the military, a refusal to consent would impact a soldier's everyday life. Would the soldiers be exempt from going into battle without INDs, or would they still be forced to go to battle but not be given the INDs?

The first time period where anticipatory consent can be obtained is during the time of recruitment (2). This time period makes the most sense, since it is during the initial recruitment phase of the soldier. At this time, soldiers sign to and agree to abide by military codes of justice and its regulations (2). During this phase, recruiting officers are able to interview and assess whether or not the candidate is willing to give anticipatory consent for the use of INDs.

At the time of recruitment, the recruiter can give the appropriate information regarding anticipatory consent, including background information and the need for INDs. Given this information, the recruit can decide for him- or herself whether or not he/she agrees to provide anticipatory consent. This is a great time to obtain consent since in an all-volunteer military the recruits are knowingly putting themselves at danger by joining the military (2). If the recruit does not agree to anticipatory consent, then he or she can choose to simply not join the military.

The problem with this is that the military may lose potentially valuable members of its force who otherwise might have joined, had there been no need for anticipatory consent. Furthermore, the military recruiter may not be the best person to obtain anticipatory consent from prospective members. This is because the recruiters may give a skewed or lightened version of the need so that they can get more recruits to sign up and achieve their quotas.

Lastly, if anticipatory consent is given at this stage it may be given without much thought and deliberation regarding the harms and dangers that the soldier may experience if INDs are required to be used (2). The duration and scope of the consent too is a problem; would the recruit be assenting for all INDs throughout his or her military career or for a designated amount of time (2)?

The second time period when it may make sense to get anticipatory consent from soldiers for the use of INDs in warfare is during the basic training phase (2). At basic training, recruits are given a lot of information regarding military policies and procedures (2). This includes training for biological and chemical weapons (2). Thus, military personnel can easily include the need to obtain anticipatory consent from the soldiers in case chemical and biological weapons are used. However, due to the fact that basic training is already packed with so many things to do, this option may not be logistically feasible (2). Furthermore, questions regarding the scope, duration, and what would happen in case of denial are all important ones that arise that have no concrete answer (2).

The third time period during which anticipatory consent may be obtained is right before deployment (2). This is the best and most viable option. If anticipatory consent is

obtained before deployment to war, the need for INDs will be apparent to all soldiers. All those involved in the conflict will know the gravity of the situation that they are getting into and the very real need to give anticipatory consent. This anticipatory consent before deployment would not be blanket consent for the rest of the soldier's life in the military, but instead would be limited in duration to the time required to fulfill the specific mission. The scope of the consent would cover the particular INDs to be used on the particular military mission the soldier is being deployed for, so there would be no confusion regarding what the soldiers would be taking. Furthermore, the content of the information given to the soldiers would be pertinent to the conflict that lay ahead and the immediate need for the use of INDs including the risks and benefits of those particular INDs.

If soldiers refuse to give consent, they could forgo deployment and instead be assigned support roles for the mission. This would allow those soldiers that give consent to go out in battle and those that do not give consent to have their rights protected without endangering their peers. In case too many soldiers refuse to give consent and there is a shortage of troops, then soldiers who declined to give consent should still be obligated to go into battle because at that point, the military has done all it can and has fulfilled its duty to protect the soldier to the best of its ability.

The question arises: how would consent be obtained? A briefing could be held by the unit's commanding officers in which the risks and benefits are clearly laid out. Then the soldiers can make their own decisions regarding the anticipatory use of INDs. The commanding officers need not go into too much detail as to scare the soldiers, but enough so that they know what they are consenting to. This would allow them to make their own

informed decision regarding whether or not to give consent. This is the best option to balance the interests the military and those of the soldier.

Anticipatory consent, however, should only be obtained if there is a need for treatment related consent prior to specific military instances and in cases where consent is not-feasible or could be waived. Routine military research and treatment should still follow regular military regulations such as the Common Rule and the Defense Appropriations Act. This distinction will allow the soldiers autonomy to be fully respected and permits anticipatory consent to be obtained as a last resort if there is a stronger justification for the need of treatments without consent.

After examining some of the alternatives to the Interim Rule, including revocation, a new military use category, and anticipatory consent, the best alternative is the adoption of anticipatory consent. The main problem with obtaining anticipatory consent stems from the soldier's ability to refuse consent. This problem could be solved with contingency plans for implementation in case too many solders decline to give consent. Anticipatory consent is the fairest alternative to the Interim Rule. It allows the needs of the military to be met while respecting the autonomy of the soldiers.

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## CHAPTER SIX

### CONCLUSIONS

The Gulf War ended swiftly in February 1991, about 60 days after the first deployments of troops (1). The prompt completion of the Gulf War would not have been possible without the Interim Rule that allowed the military to administer preventative therapies to help protect the troops. The Interim Rule, though, has numerous shortcomings which will be addressed in this chapter. I will also offer information about the current status of the Interim Rule and a short conclusion.

#### *Shortcomings of the Interim Rule*

One of the biggest issues with the Interim Rule was that it did not adequately address the issue of informed consent. The importance of obtaining consent from soldiers is not even mentioned in the Rule. There is a presumption in the Interim Rule that consent is not required or important (2). When the FDA commissioner judges that “actual or threatened” combat circumstances may dictate the use of INDs and there “is no available satisfactory alternative therapy,” the right of Military Personnel to informed consent can be immediately taken away (3). The Interim Rule needs to address the importance of consent. The presumption should be in favor of obtaining consent, rather than allowing it to be waived due to combat exigencies.

A second shortcoming of the Interim Rule was the failure to require a disinterested IRB to review the application for the waiver of informed consent. The Rule

did include a requirement to have an IRB formally review and approve the protocol of using INDs without consent, but the Rule did not specify that an independent IRB or one that is not connected to the DoD was required in order to avoid a conflict of interest. For example, when the DoD initially requested waivers for the use of INDs, it requested a waiver for a third drug, Multi-Shield (2). This drug was an experimental burn cream and was expected to hasten the healing of burns (2). The DoD applied for the waiver after its IRB had approved the drug for use without consent during the Gulf War. Presumably, the IRB was satisfied with the safety and efficacy of the drug. After the application for the waiver was filed, however, further animal studies showed that the drug had some potentially very serious side effects (2).

The drug induced skin irritation so severe that the officials believed that the desire to itch would overwhelm the soldiers and harm them instead (2). The application for the waiver was later withdrawn by the DoD because of this (2). The Multi-Shield example shows that the DoD's IRB had the potential for misuse and to act as a mere "rubber stamp" in approving whatever protocols the DoD brought forth. There needs to be an independent, disinterested IRB that is not composed mainly of military members to review military proposals objectively and determine what is best for the subjects and not the military.

Finally, there was a problem with the Interim Rule's requirement to distribute information regarding the drugs to the troops. As part of the discussions for the Interim Rule, the FDA mandated the DoD to provide information to the soldiers regarding the drugs that they would be taking (4). During the buildup to the war, the DoD and the FDA worked on creating handouts that contained information regarding the expected benefits,

interactions, and any known side effects of the drugs. Upon deployment, however, most of the troops did not receive the information as required, including, oral and written, about the drugs that they were being forced to take.

One of the explanations for this lack of information given by the DoD was that information was not distributed because they did not want Iraqi intelligence to learn that the soldiers had protection in case the biological or chemical weapons were used (2). This explanation was later retracted and another was given stating that the DoD could not fulfill its obligations because the information sheets did not reach the Gulf (2).

This information could have been critical to the troops. If the DoD had provided information to the troops, it would have extended at least some level of respect to the troops (2). Instead, the troops were uninformed and instructed to do as told by their commanding officers. Furthermore, the dissemination of information would have enabled the troops to know if they would have any side effects from the drugs and when to seek help, especially if they over dosed or missed a dosage of the drugs (2). If nothing else, by giving information sheets to the troops, the DoD would help boost the morale of the troops since they would know what they are taking (2). This increased psychological benefit could have helped the military achieve the mission faster, since the troops may have been more motivated. Some of these shortcomings were addressed in the follow up to the Interim Rule, as the Interim Rule was never meant to be permanent.

### ***Final Rule***

In 1996, the DoD requested that the FDA issue a blanket waiver of consent for the military to allow the use of INDs (5). This request, however, was denied by the FDA, which passed a new Final Rule in 1999 (5).

In October 1999, the FDA repealed the previous Interim Rule and passed the Final Rule to take its place. The Final Rule essentially still allows the use of INDs but there are a couple major differences between it and the original Interim Rule. In the original rule of 1990, the FDA commissioner was the approving authority for the waivers of consent that were requested. This changed in 1999; now the president of the United States is the approving authority for waivers of consent (5). The Final rule states that the President of the United States can approve the waiving of informed consent if he or she finds that “obtaining informed consent is 1) not feasible, 2) contrary to the best interests of the member, or 3) not in the interests of national security” (6, 5). Notably, there was no change in the rule’s failure to mention the importance of informed consent for soldiers.

Along with this change, several other important changes were made to the prior Interim Rule. The Final Rule requires the distribution of an information sheet for each investigational drug to every service member (6). The information sheet is required to list the fact that the drug is investigational, its benefits and risks, and possible side effects. This change is in direct contrast to the Interim Rule, in which the IRB recommended that these information sheets be given, but there was no law specifying that they had to be distributed.

Another change that the Final Rule contains is that the DoD will be required to provide information to the public in the Federal Registrar (as soon as it is practical)

regarding every case for which it petitions the use of INDs (5). The information would be required to include summaries of relevant scientific data and other pertinent information regarding the use of the INDs (6, 5). This is important as it establishes transparency to deter the misuse of INDs and also allows the public to know what the soldiers are being given and hopefully will help allay public fears.

Finally, in the prior Interim Rule, the DoD used a couple of different IRBs to seek the approval for the protocol to waive informed consent. The manipulation of IRBs was of extreme concern to the FDA and therefore the Final Rule set out to correct that (5). The Final Rule required any IRB that is convened by the military to evaluate an IND protocol to have at least three members who are not employees of the federal government, and are not connected in any way to the protocol (6, 5). Furthermore, if the multiple IRBs are to be convened the notes and minutes from the previous IRB meetings must be given and considered by the new IRB in its decision (6, 5).

The Final Interim Rule addressed some of the issues and shortcomings of the Interim Rule. However, in my opinion the Final Rule is still lacking in respecting the autonomy of soldiers and allowing them to make decisions regarding the use of INDs. The new Final Rule is just slightly improved and when INDs will need to be used in the future, I do not think there will be any less controversy regarding the legitimacy of waiving consent by the military.

### ***Conclusion***

The regulatory rules of the FDA stated that obtaining consent was necessary because the INDs were being used by the DoD in an unapproved capacity. However, this

did not necessarily mean that the rights of the soldiers were being violated when they were given INDs without their consent through the use of the Interim Rule.

There are two arguments regarding why consent should have been obtained. The first argument was that the use of INDs constituted research. This argument does not hold because the nature of the intervention is purely therapeutic and is further refuted by the Belmont Report which states that “even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research” (7).

The second argument was that consent should have been obtained for the use of unproven therapies. However, this need for consent for the use of unproven therapies is also overridden when we examine the ethical principles behind the DoD’s decision. Even though the waiver of consent does override the individual soldier’s choice in accepting or denying treatment, it is necessary for the protection of all the soldiers in battle. If the DoD allowed the soldiers a choice in the matter, it is possible that soldiers would have refused the pretreatment. The decision by soldiers to forgo pretreatment could be very detrimental to both fellow soldiers and the mission itself. This is because the soldiers who denied themselves the pretreatments may be quicker to fall in the face of chemical and biological weapons and this would ultimately endanger the lives of the other soldiers. It is the paternalistic relationship between the DoD and the underlying principle of beneficence that necessitates the administration of INDs. If the troops were not administered the INDs, it is possible that many soldiers would needlessly be put in harm’s way from the exposure to chemical and biological weapons used by Iraqi forces.

Ideally, the autonomy of soldiers should be fully protected and there should be an obligation to obtain informed consent, but I think this is impractical in the military. Wars will continue and INDs will continue to be needed and used by Military personnel. The soldiers who have volunteered to serve need to be given the best treatments possible in order to prevent harm and complete the task at hand. By forcing soldiers to take INDs, the DoD is fulfilling its ethical obligations. Perhaps in the future, if respect for a soldier's autonomy is given greater weight, the implementation of anticipatory consent will be given serious consideration. Until then, precautions have to be taken in order to protect those who sacrifice their lives by serving the military.

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